Image AF/1654

PATENT
Customer No. 22,852
Attorney Docket No. 06478.1462

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	
Jürgen RÖMISCH et. al.	Group Art Unit: 1654
Application No.: 10/033,777	Examiner: Michael V. Meller
Filed: January 3, 2002	
For: STABILIZED LIQUID PREPARATION OF THE PROTEASE WHICH ACTIVATES BLOOD COAGULATION FACTOR VII, OR OF ITS PROENZYME	

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TRANSMITTAL OF APPEAL BRIEF (37 C.F.R. 1.192)

Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on October 23, 2003.

This application is on behalf of

☐ Small Entity ☒ Large Entity

Pursuant to 37 C.F.R. 1.17(f), the fee for filing the Appeal Brief is:

☐ $165.00 (Small Entity)

☒ $330.00 (Large Entity)

TOTAL FEE DUE:

Total Fee Due $330.00

☒ Enclosed is a check for $330.00 to cover the above fees.

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PETITION FOR EXTENSION:

If any extension of time is necessary for the filing of this Appeal Brief, and such extension has not otherwise been requested, such an extension is hereby requested, and the Commissioner is authorized to charge necessary fees for such an extension to our Deposit Account No. 06-0916. A duplicate copy of this paper is enclosed for use in charging the deposit account.

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 18, 2003

By: _____
Sanya Sukduang
Reg. No. 46,390

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APPEAL BRIEF UNDER 37 C.F.R. § 1.192

In support of the Notice of Appeal filed on October 23, 2003, and pursuant to 37 C.F.R. § 1.192, Appellants present three copies of their brief and a check in the amount of $330.00 for the fee under 37 C.F.R. § 1.17(c). Please grant any extensions of time required to enter this Appeal Brief and charge any additional required fees to our Deposit Account No. 06-0916.

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I. Real Party In Interest

The real party in interest is Aventis Behring GmbH, Assignee of the present application. The assignment was recorded on April 18, 2002, at Reel 012806, Frame 0640.

II. Related Appeals and Interferences

To the best of the undersigned's knowledge, there are no related appeals or interferences known to Appellants, the Appellants' legal representative, or Assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

III. Status Of Claims

Claims 1-24 were originally filed in this application. The Examiner withdrew claims 22-24 as non-elected in the Office Action mailed January 14, 2003. Thus, claims 1-21 are currently pending.

IV. Status Of Amendments

The amendment of claim 1, filed on April 10, 2003, has been entered. *See* Advisory Action mailed October 7, 2003, at 1-2. Appendix A presents the claims in the form pending after that Amendment.

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V. Summary Of Invention

Appellants have invented a novel, stabilized liquid preparation comprising a protease, or its proenzyme, that activates blood coagulation factor VII.[1] The invention therefore relates to stabilized preparations, as well as methods of treatment and diagnosis using these preparations.

The physical and chemical instabilities of proteins, including proteases, make it difficult to store and use preparations containing these proteins efficiently. Proteases are generally fragile, unstable molecules that can inactivate rapidly through several mechanisms, such as proteolysis, deamidation, oxidation, racemization, beta-elimination, aggregation, precipitation, denaturation, and adsorption to surfaces. Appellants observed, for instance, "a rapid loss of activity" after the enrichment or isolation of a protease that activates coagulation factor VII. *See* Specification at 2, ¶ 3. Further complicating matters, proteins possess unique chemical and physical properties, which pose a problem in identifying stabilizing methods for preparations containing them.

The present invention solves the problem of protease instability by disclosing a novel, stabilized protease or proenzyme preparation. The disclosed and claimed stabilized liquid preparation containing a protease or proenzyme "can be stored for several months without showing significant losses of activity or changes in the product." *See* Specification at 2, ¶ 1.

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[1] Blood clotting requires the activation of various coagulation factors. Many of these factors circulate in the blood as inactive precursors or proenzymes until they are activated by proteolytic cleavage. Coagulation proceeds in a cascade-like fashion. The activation of one proenzyme commonly creates an enzyme that activates a second proenzyme and so on.

The stabile liquid preparations can be used, for example, "as procoagulants either alone or together with substances which increase protease activity . . . ," and can be administered intravenously, locally, subcutaneously, intradermally, intramuscularly, topically or bound to a suitable matrix. *See* Specification at 4, ¶ 13 and 5, ¶ 16. Maintaining biological activity of a protease is important when proteases are part of pharmaceutical compositions. Thus, the stabilized liquid preparations of the invention may also be used optimally and efficiently in the "general prophylaxis of bleeding or for stopping hemorrhages." Specification at 5, ¶ 13.

Claim 1, the only independent claim, is directed to a stabilized liquid preparation comprising a protease or its proenzyme, wherein the protease or its proenzyme activates blood coagulation factor VII. The stabilized liquid preparation of claim 1 also includes at least one compound selected from the group consisting of ornithine, diaminopimelic acid, agmatine, creatine, guanidinoacetic acid, acetylornithine, citrulline, argininosuccinic acid, tranexamic acid, and ε-aminocaproic acid or their salts and derivatives. The pH of the stabilized liquid preparation of claim 1 is from 2.0 to 8.0. Support for claim 1 can be found throughout the Specification and specifically at 3, ¶ 7.

Claims 2-5 further limit claim 1 by adding to the stabilized liquid preparation an ionic or nonionic detergent (claims 2-3) in amounts ranging from 0.001 to 0.5 % by weight (claims 4-5). Support for claims 2-5 can be found at 3, ¶ 9.

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Claims 6 and 7 further specify that the pH of the stabilized liquid preparation is in the range of 2.5 to 6.8 and 3.5 to 6.8. Support for claims 6-7 is found in the Specification at 3, ¶ 7.

Claim 8, which depends from claim 1, states that the stabilized liquid preparation additionally comprises at least one detergent, at least one sugar, at least one amino acid, and optionally, at least one compound capable of calcium ion complexation. Support for claim 8 is found in the Specification at 3, ¶ 8.

Claims 9-11 depend from claim 8 and identify the detergent as either an ionic or nonionic detergent (claims 9-10) and specifies that the detergent is present in an amount from 0.001 to 0.5% by weight. Support for claims 9-11 can be found in the Specification at 3, ¶ 9.

Claim 12 states that the at least one sugar of claim 8 is selected from glucose, arabinose, and mannose. Claim 12 is supported at 4, ¶ 11 of the Specification.

Claim 13 states that the at least one amino acid of claim 8 is selected from arginine, lysine and glycine. Claim 13 is supported at 4, ¶ 12 of the Specification.

Claims 14 and 15, which depend from claims 1 and 8 respectively, claim the stabilized liquid preparation wherein the ionic strength of the preparation is adjusted to greater than 10 mSi by the addition of a salt. These claims are supported at 4, ¶ 10 of the Specification.

Claims 16 and 17, which also depend from claims 1 and 8 respectively, claim the stabilized liquid preparation wherein the protease or its proenzyme is in

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lyophilized form. Support for claims 16-17 can be found in the Specification at 3-4, ¶ 10.

Claims 18 and 19, depending from claims 1 and 8 respectively, claim the stabilized liquid preparation wherein the protease or its proenzyme is present in an amount greater than 0.5 mg/ml. *See* Specification at 4, ¶ 10.

Claim 20 is directed to a pharmaceutical composition comprising the stabilized liquid preparation of claim 1. Claim 20 is supported in the Specification at 4-5, ¶¶ 13-16.

Finally, claim 21 is directed to a diagnostic reagent comprising the stabilized liquid preparation of claim 10. Claim 21 is supported in the Specification at 4-5, ¶¶ 13-16.

A description of the Appellants' invention cannot be derived from the disclosure of the alleged prior art.

VI. Issue

Whether claims 1-21 are non-obvious and patentable under 35 U.S.C. § 103(a) over Japanese Publication No. 2000-023696 or European Patent EP 0 952 215 taken with *Sato et al.* (U.S. Patent No. 4,465,662) and further in view of *Roy et al.* (U.S. Patent No. 5,589,363) or *Kessler et al.*(U.S. Patent No. 5,604,202).

VII. Grouping Of Claims

For the purposes of this appeal, claims 1-21 stand or fall together.

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VIII. Argument

In the Final Office Action, claims 1-21 under 35 U.S.C. § 103(a) were rejected over Japanese Publication No. 2000-023696 or European Patent EP 0 952 215 taken with *Sato et al.* (U.S. Patent No. 4,465,662) and further in view of *Roy et al.* (U.S. Patent No. 5,589,363) or *Kessler et al.* (U.S. Patent No. 5,604,202).[2] *See* Final Office Action mailed June 26, 2003, at 3. The entire basis given for the Examiner's rejection is that "[i]t is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art." *Id.* The Examiner concludes by stating "since the individual ingredients are known in the art to be used individually for the same purpose, to use them together is obvious." *Id.* The Appellants respectfully assert that the Examiner has not met the initial burden of establishing a *prima facie* case of obviousness. Accordingly, Appellants request that the rejection of claims 1-21 be reversed.

A *prima facie* case of obviousness is met only if: (1) all claim limitations are taught or suggested, (2) there is some suggestion or motivation to modify the references or combine reference teachings, and (3) there is a reasonable expectation of success. *See* M.P.E.P. § 2143. Further, the initial burden is on the Examiner to establish these three basic criteria. *See, e.g., Ex parte Blanc*, 13 U.S.P.Q.2d (BNA)

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[2] Appellants note that the Examiner did not maintain nor did he withdraw the rejections made in the first Office Action mailed January 14, 2003, in subsequent Office Actions. Appellants stated in their response of September 8, 2003, that the rejections made in the first Office Action were presumed withdrawn. The Examiner did not reinstate those rejections in the Advisory Action mailed October 7, 2003 and, therefore, those rejections are presumed withdrawn and not addressed here.

1383, 1384 (Bd. Pat. App. & Inter. 1989) (finding "[b]y setting forth such a broad-brush statement and by failing to explain with a reasonable degree of specificity any one rejection, the examiner has failed, procedurally, to establish a prima facie case of obviousness"); *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Inter. 1986) (finding "[w]hen the incentive to combine the teachings of the references is not readily apparent, it is the duty of the examiner to explain why combination of the reference teachings is proper").

Section 706.02(j) of the M.P.E.P. also highlights the importance of the Examiner's initial duty, stating that "[i]t is important for an examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply." Further, when the claims are rejected under 35 U.S.C. § 103 the Examiner should set forth in the Office Action:

> (A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,
>
> (B) the difference or differences in the claim over the applied reference(s),
>
> (C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and
>
> (D) an explanation why one of ordinary skill in the art at the time of the invention was made would have been motivated to make the proposed modification.

M.P.E.P § 706.02(j).

In the present case, the Examiner has not set forth any of these four elements, nor met any of the three basic criteria needed to establish a *prima facie* case of obviousness. In the final Office Action, the Examiner newly cited four references,

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including two new primary references, JP 2000-023696 and EP 0 922 215, without setting forth the relevant teachings of the alleged prior art relied upon. *See* Final Office Action mailed June 26, 2003, at 3. The Examiner has also failed to set forth what parts of the five references are relied upon (*i.e.*, there are no references to either column or page number), the differences between the claimed invention and the applied references, the proposed modification of the applied references necessary to arrive at the claimed invention, or why one of skill in the art would be motivated to modify the references to arrive at the claimed invention. *See* M.P.E.P. § 706.02(j). Without any identification or explanation from the Examiner, the reasons or incentives to combine the teachings of the references to achieve the claimed invention are not readily apparent and it is not cleat how the five references are linked.

As stated above, the entire basis given for the Examiner's rejection is that "it is obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose." Final Office Action at 3. However, the Examiner has not stated what that purpose is nor how the prior art has taught that the separate ingredients are useful for the same purpose. *See Ex Parte Clapp*, 227 USPQ at 973; *Ex parte Skinner*, 2 U.S.P.Q.2d at 1790.

The Examiner also stated that "[t]he idea for combining them flows logically from their having been used individually in the prior art." But combination of individual ingredients is not necessarily logical even when the claimed purpose is close to that found in the prior art. In *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d (BNA) 1276 (Fed. Cir. 1987), the Federal Circuit found no suggestion to combine three ingredients in

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one composition for the purpose of inhibiting scaling and corrosion in a cooling water system even when all three ingredients had appeared in the prior art, albeit in different combinations of the ingredients, in compositions for preventing scale in boiling and cooling systems. The court rejected the PTO's finding of a *prima facie* case of obviousness stating, "[a]t best in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103." *In re Geiger*, 815 F.2d at 688, 2 U.S.P.Q. 2d at 1278. In *Geiger*, the Federal Circuit rejected the idea that combining ingredients flows logically from their having been used individually in the prior art even for the same purpose.

Although the Examiner failed to sufficiently enunciate a reasonable basis for the § 103 rejection, it is clear that the references, when combined, do not render the claimed invention obvious. While JP 2000-023696 and EP 0 922 215 disclose a protease or proenzyme capable of activating blood coagulation factor VII, the two primary references fail to teach or suggest all of the claimed elements.[3] Specifically, the references fail to disclose the compounds recited in subpart (b) of claim 1 or the addition of an ionic or nonionic detergent, as recited in at least claims 2-3. The secondary references, *Roy et al.*, *Kessler et al.* and *Sato et al.* do not cure these defects as none of the references teach the use of their respective subject matters with the protease or proenzyme which activates blood clotting factor VII.

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[3] JP 2000-023696 and EP 0 922 2153 are essentially the same reference as they describe the same invention and both depend from the same German priority documents.

The Examiner previously relied on *Sato et al.* as a secondary reference in the first Office Action of January 14, 2003, to disclose "that tranexamic acid can be used with a protease at a pH between 2-8[.]" Appellants respectfully submit that this reference, which discloses an oral composition of tranexamic acid, does not teach or suggest the use of tranexamic acid with a protease capable of activating blood coagulation factor VII or its proenzyme, which is an element of the claimed invention. *See* Appendix A, claim 1. Rather, *Sato et al.* discloses the use of tranexamic acid as a periodontosis prophylaxis, *see Sato et al.*, column 1, lines 8-13, not as a stabilizer as disclosed in the present invention. *Sato et al.* further states that "[a]n additional disadvantage of such tranexamic acid-containing oral compositions is that they are unstable." *See Sato et al.*, col. 1, ll. 18-19 (emphasis added). Thus, it is unclear how the Examiner is relying on *Sato et al.* and it is even more unclear how *Sato et al.* would be combined with the other cited references to establish a *prima facie* case of obviousness of the claimed invention which is to a stabilized liquid preparation.

The Examiner has not clearly set forth any reasoning for the rejection of the pending claims under 35 U.S.C. § 103 nor is such reasoning readily apparent. Further, the initial burden of the Examiner to establish a *prima facie* case of obviousness has not been met. Thus, Appellants respectfully request the rejection be reversed.

CONCLUSION

If any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any fees

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required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 18, 2003

By: _____
Sanya Sukduang
Reg. No. 46,390

Post Office Address (to which correspondence is to be sent)

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Appendix A

1. (Previously Presented) A stabilized liquid preparation comprising:

a. a protease or its proenzyme, wherein the protease or its proenzyme activates blood coagulation factor VII;

b. at least one compound selected from the group consisting of ornithine, diaminopimelic acid, agmatine, creatine, guanidinoacetic acid, acetylornithine, citrulline, argininosuccinic acid, tranexamic acid, and ε-aminocaproic acid or their salts and derivatives; and

c. wherein said preparation has a pH from 2.0 to 8.0.

2. (Original) The stabilized liquid preparation of claim 1, which additionally comprises at least one ionic detergent.

3. (Original) The stabilized liquid preparation of claim 1, which additionally comprises at least one nonionic detergent.

4. (Original) The stabilized liquid preparation of claim 2, wherein the ionic detergent is present in an amount ranging from 0.001 to 0.5 percent by weight of the liquid preparation.

5. (Original) The stabilized liquid preparation of claim 3, wherein the nonionic detergent is present in an amount ranging from 0.001 to 0.5 percent by weight of the liquid preparation.

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6. (Original) The stabilized liquid preparation of claim 1, wherein the pH is between 2.5 and 6.8.

7. (Original) The stabilized liquid preparation of claim 1, wherein the pH is between 3.5 and 6.8.

8. (Original) The stabilized liquid preparation of claim 1, wherein the liquid preparation additionally comprises:

a. at least one detergent;

b. at least one sugar;

c. at least one amino acid; and optionally

d. at least one compound capable of calcium ion complexation.

9. (Original) The stabilized liquid preparation of claim 8, wherein the detergent is at least one ionic detergent.

10. (Original) The stabilized liquid preparation of claim 8, wherein the detergent is at least one nonionic detergent.

11. (Original) The stabilized liquid preparation of claim 8, wherein the detergent is present in an amount from 0.001 to 0.5 percent by weight of the liquid preparation.

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12. (Original) The stabilized liquid preparation of claim 8, wherein the at least one sugar is selected from glucose, arabinose, and mannose.

13. (Original) The stabilized liquid preparation of claim 8, wherein the at least one amino acid is selected from arginine, lysine, and glycine.

14. (Original) The stabilized liquid preparation of claim 1, wherein the ionic strength of the liquid preparation is adjusted to greater than 10 mSi by the addition of a salt.

15. (Original) The stabilized liquid preparation of claim 8, wherein the ionic strength of the liquid preparation is adjusted to greater than 10 mSi by the addition of a salt.

16. (Original) The stabilized liquid preparation of claim 1, wherein the protease or its proenzyme is in lyophilized form.

17. (Original) The stabilized liquid preparation of claim 8, wherein the protease or its proenzyme is in lyophilized form.

18. (Original) The stabilized liquid preparation of claim 1, wherein the protease or its proenzyme is present in an amount greater than 0.5 mg/ml.

19. (Original) The stabilized liquid preparation of claim 8, wherein the protease or its proenzyme is present in an amount greater than 0.5 mg/ml.

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20. (Original) A pharmaceutical composition comprising the stabilized liquid preparation of claim 1.

21. (Original) A diagnostic reagent comprising the stabilized liquid preparation of claim 10.

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The present invention solves the problem of protease instability by disclosing a novel, stabilized protease or proenzyme preparation. The disclosed and claimed stabilized liquid preparation containing a protease or proenzyme "can be stored for several months without showing significant losses of activity or changes in the product." *See* Specification at 2, ¶ 1.

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[1] Blood clotting requires the activation of various coagulation factors. Many of these factors circulate in the blood as inactive precursors or proenzymes until they are activated by proteolytic cleavage. Coagulation proceeds in a cascade-like fashion. The activation of one proenzyme commonly creates an enzyme that activates a second proenzyme and so on.

The stabile liquid preparations can be used, for example, "as procoagulants either alone or together with substances which increase protease activity . . . ," and can be administered intravenously, locally, subcutaneously, intradermally, intramuscularly, topically or bound to a suitable matrix. *See* Specification at 4, ¶ 13 and 5, ¶ 16. Maintaining biological activity of a protease is important when proteases are part of pharmaceutical compositions. Thus, the stabilized liquid preparations of the invention may also be used optimally and efficiently in the "general prophylaxis of bleeding or for stopping hemorrhages." Specification at 5, ¶ 13.

Claim 1, the only independent claim, is directed to a stabilized liquid preparation comprising a protease or its proenzyme, wherein the protease or its proenzyme activates blood coagulation factor VII. The stabilized liquid preparation of claim 1 also includes at least one compound selected from the group consisting of ornithine, diaminopimelic acid, agmatine, creatine, guanidinoacetic acid, acetylornithine, citrulline, argininosuccinic acid, tranexamic acid, and ε-aminocaproic acid or their salts and derivatives. The pH of the stabilized liquid preparation of claim 1 is from 2.0 to 8.0. Support for claim 1 can be found throughout the Specification and specifically at 3, ¶ 7.

Claims 2-5 further limit claim 1 by adding to the stabilized liquid preparation an ionic or nonionic detergent (claims 2-3) in amounts ranging from 0.001 to 0.5 % by weight (claims 4-5). Support for claims 2-5 can be found at 3, ¶ 9.

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Claims 6 and 7 further specify that the pH of the stabilized liquid preparation is in the range of 2.5 to 6.8 and 3.5 to 6.8. Support for claims 6-7 is found in the Specification at 3, ¶ 7.

Claim 8, which depends from claim 1, states that the stabilized liquid preparation additionally comprises at least one detergent, at least one sugar, at least one amino acid, and optionally, at least one compound capable of calcium ion complexation. Support for claim 8 is found in the Specification at 3, ¶ 8.

Claims 9-11 depend from claim 8 and identify the detergent as either an ionic or nonionic detergent (claims 9-10) and specifies that the detergent is present in an amount from 0.001 to 0.5% by weight. Support for claims 9-11 can be found in the Specification at 3, ¶ 9.

Claim 12 states that the at least one sugar of claim 8 is selected from glucose, arabinose, and mannose. Claim 12 is supported at 4, ¶ 11 of the Specification.

Claim 13 states that the at least one amino acid of claim 8 is selected from arginine, lysine and glycine. Claim 13 is supported at 4, ¶ 12 of the Specification.

Claims 14 and 15, which depend from claims 1 and 8 respectively, claim the stabilized liquid preparation wherein the ionic strength of the preparation is adjusted to greater than 10 mSi by the addition of a salt. These claims are supported at 4, ¶ 10 of the Specification.

Claims 16 and 17, which also depend from claims 1 and 8 respectively, claim the stabilized liquid preparation wherein the protease or its proenzyme is in

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lyophilized form. Support for claims 16-17 can be found in the Specification at 3-4, ¶ 10.

Claims 18 and 19, depending from claims 1 and 8 respectively, claim the stabilized liquid preparation wherein the protease or its proenzyme is present in an amount greater than 0.5 mg/ml. *See* Specification at 4, ¶ 10.

Claim 20 is directed to a pharmaceutical composition comprising the stabilized liquid preparation of claim 1. Claim 20 is supported in the Specification at 4-5, ¶¶ 13-16.

Finally, claim 21 is directed to a diagnostic reagent comprising the stabilized liquid preparation of claim 10. Claim 21 is supported in the Specification at 4-5, ¶¶ 13-16.

A description of the Appellants' invention cannot be derived from the disclosure of the alleged prior art.

VI. Issue

Whether claims 1-21 are non-obvious and patentable under 35 U.S.C. § 103(a) over Japanese Publication No. 2000-023696 or European Patent EP 0 952 215 taken with *Sato et al.* (U.S. Patent No. 4,465,662) and further in view of *Roy et al.* (U.S. Patent No. 5,589,363) or *Kessler et al.*(U.S. Patent No. 5,604,202).

VII. Grouping Of Claims

For the purposes of this appeal, claims 1-21 stand or fall together.

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VIII. Argument

In the Final Office Action, claims 1-21 under 35 U.S.C. § 103(a) were rejected over Japanese Publication No. 2000-023696 or European Patent EP 0 952 215 taken with *Sato et al.* (U.S. Patent No. 4,465,662) and further in view of *Roy et al.* (U.S. Patent No. 5,589,363) or *Kessler et al.* (U.S. Patent No. 5,604,202).[2] *See* Final Office Action mailed June 26, 2003, at 3. The entire basis given for the Examiner's rejection is that "[i]t is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art." *Id.* The Examiner concludes by stating "since the individual ingredients are known in the art to be used individually for the same purpose, to use them together is obvious." *Id.* The Appellants respectfully assert that the Examiner has not met the initial burden of establishing a *prima facie* case of obviousness. Accordingly, Appellants request that the rejection of claims 1-21 be reversed.

A *prima facie* case of obviousness is met only if: (1) all claim limitations are taught or suggested, (2) there is some suggestion or motivation to modify the references or combine reference teachings, and (3) there is a reasonable expectation of success. *See* M.P.E.P. § 2143. Further, the initial burden is on the Examiner to establish these three basic criteria. *See, e.g., Ex parte Blanc*, 13 U.S.P.Q.2d (BNA)

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[2] Appellants note that the Examiner did not maintain nor did he withdraw the rejections made in the first Office Action mailed January 14, 2003, in subsequent Office Actions. Appellants stated in their response of September 8, 2003, that the rejections made in the first Office Action were presumed withdrawn. The Examiner did not reinstate those rejections in the Advisory Action mailed October 7, 2003 and, therefore, those rejections are presumed withdrawn and not addressed here.

1383, 1384 (Bd. Pat. App. & Inter. 1989) (finding "[b]y setting forth such a broad-brush statement and by failing to explain with a reasonable degree of specificity any one rejection, the examiner has failed, procedurally, to establish a prima facie case of obviousness"); *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Inter. 1986) (finding "[w]hen the incentive to combine the teachings of the references is not readily apparent, it is the duty of the examiner to explain why combination of the reference teachings is proper").

Section 706.02(j) of the M.P.E.P. also highlights the importance of the Examiner's initial duty, stating that "[i]t is important for an examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply." Further, when the claims are rejected under 35 U.S.C. § 103 the Examiner should set forth in the Office Action:

> (A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,
>
> (B) the difference or differences in the claim over the applied reference(s),
>
> (C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and
>
> (D) an explanation why one of ordinary skill in the art at the time of the invention was made would have been motivated to make the proposed modification.

M.P.E.P § 706.02(j).

In the present case, the Examiner has not set forth any of these four elements, nor met any of the three basic criteria needed to establish a *prima facie* case of obviousness. In the final Office Action, the Examiner newly cited four references,

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including two new primary references, JP 2000-023696 and EP 0 922 215, without setting forth the relevant teachings of the alleged prior art relied upon. *See* Final Office Action mailed June 26, 2003, at 3. The Examiner has also failed to set forth what parts of the five references are relied upon (*i.e.*, there are no references to either column or page number), the differences between the claimed invention and the applied references, the proposed modification of the applied references necessary to arrive at the claimed invention, or why one of skill in the art would be motivated to modify the references to arrive at the claimed invention. *See* M.P.E.P. § 706.02(j). Without any identification or explanation from the Examiner, the reasons or incentives to combine the teachings of the references to achieve the claimed invention are not readily apparent and it is not cleat how the five references are linked.

As stated above, the entire basis given for the Examiner's rejection is that "it is obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose." Final Office Action at 3. However, the Examiner has not stated what that purpose is nor how the prior art has taught that the separate ingredients are useful for the same purpose. *See Ex Parte Clapp*, 227 USPQ at 973; *Ex parte Skinner*, 2 U.S.P.Q.2d at 1790.

The Examiner also stated that "[t]he idea for combining them flows logically from their having been used individually in the prior art." But combination of individual ingredients is not necessarily logical even when the claimed purpose is close to that found in the prior art. In *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d (BNA) 1276 (Fed. Cir. 1987), the Federal Circuit found no suggestion to combine three ingredients in

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one composition for the purpose of inhibiting scaling and corrosion in a cooling water system even when all three ingredients had appeared in the prior art, albeit in different combinations of the ingredients, in compositions for preventing scale in boiling and cooling systems. The court rejected the PTO's finding of a *prima facie* case of obviousness stating, "[a]t best in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103." *In re Geiger*, 815 F.2d at 688, 2 U.S.P.Q. 2d at 1278. In *Geiger*, the Federal Circuit rejected the idea that combining ingredients flows logically from their having been used individually in the prior art even for the same purpose.

Although the Examiner failed to sufficiently enunciate a reasonable basis for the § 103 rejection, it is clear that the references, when combined, do not render the claimed invention obvious. While JP 2000-023696 and EP 0 922 215 disclose a protease or proenzyme capable of activating blood coagulation factor VII, the two primary references fail to teach or suggest all of the claimed elements.[3] Specifically, the references fail to disclose the compounds recited in subpart (b) of claim 1 or the addition of an ionic or nonionic detergent, as recited in at least claims 2-3. The secondary references, *Roy et al.*, *Kessler et al.* and *Sato et al.* do not cure these defects as none of the references teach the use of their respective subject matters with the protease or proenzyme which activates blood clotting factor VII.

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[3] JP 2000-023696 and EP 0 922 2153 are essentially the same reference as they describe the same invention and both depend from the same German priority documents.

The Examiner previously relied on *Sato et al.* as a secondary reference in the first Office Action of January 14, 2003, to disclose "that tranexamic acid can be used with a protease at a pH between 2-8[.]" Appellants respectfully submit that this reference, which discloses an oral composition of tranexamic acid, does not teach or suggest the use of tranexamic acid with a protease capable of activating blood coagulation factor VII or its proenzyme, which is an element of the claimed invention. *See* Appendix A, claim 1. Rather, *Sato et al.* discloses the use of tranexamic acid as a periodontosis prophylaxis, *see Sato et al.*, column 1, lines 8-13, not as a stabilizer as disclosed in the present invention. *Sato et al.* further states that "[a]n additional disadvantage of such tranexamic acid-containing oral compositions is that they are unstable." *See Sato et al.*, col. 1, ll. 18-19 (emphasis added). Thus, it is unclear how the Examiner is relying on *Sato et al.* and it is even more unclear how *Sato et al.* would be combined with the other cited references to establish a *prima facie* case of obviousness of the claimed invention which is to a stabilized liquid preparation.

The Examiner has not clearly set forth any reasoning for the rejection of the pending claims under 35 U.S.C. § 103 nor is such reasoning readily apparent. Further, the initial burden of the Examiner to establish a *prima facie* case of obviousness has not been met. Thus, Appellants respectfully request the rejection be reversed.

CONCLUSION

If any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any fees

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required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,
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Dated: December 18, 2003

By: _____
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Appendix A

1. (Previously Presented) A stabilized liquid preparation comprising:

a. a protease or its proenzyme, wherein the protease or its proenzyme activates blood coagulation factor VII;

b. at least one compound selected from the group consisting of ornithine, diaminopimelic acid, agmatine, creatine, guanidinoacetic acid, acetylornithine, citrulline, argininosuccinic acid, tranexamic acid, and ε-aminocaproic acid or their salts and derivatives; and

c. wherein said preparation has a pH from 2.0 to 8.0.

2. (Original) The stabilized liquid preparation of claim 1, which additionally comprises at least one ionic detergent.

3. (Original) The stabilized liquid preparation of claim 1, which additionally comprises at least one nonionic detergent.

4. (Original) The stabilized liquid preparation of claim 2, wherein the ionic detergent is present in an amount ranging from 0.001 to 0.5 percent by weight of the liquid preparation.

5. (Original) The stabilized liquid preparation of claim 3, wherein the nonionic detergent is present in an amount ranging from 0.001 to 0.5 percent by weight of the liquid preparation.

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6. (Original) The stabilized liquid preparation of claim 1, wherein the pH is between 2.5 and 6.8.

7. (Original) The stabilized liquid preparation of claim 1, wherein the pH is between 3.5 and 6.8.

8. (Original) The stabilized liquid preparation of claim 1, wherein the liquid preparation additionally comprises:

a. at least one detergent;

b. at least one sugar;

c. at least one amino acid; and optionally

d. at least one compound capable of calcium ion complexation.

9. (Original) The stabilized liquid preparation of claim 8, wherein the detergent is at least one ionic detergent.

10. (Original) The stabilized liquid preparation of claim 8, wherein the detergent is at least one nonionic detergent.

11. (Original) The stabilized liquid preparation of claim 8, wherein the detergent is present in an amount from 0.001 to 0.5 percent by weight of the liquid preparation.

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12. (Original) The stabilized liquid preparation of claim 8, wherein the at least one sugar is selected from glucose, arabinose, and mannose.

13. (Original) The stabilized liquid preparation of claim 8, wherein the at least one amino acid is selected from arginine, lysine, and glycine.

14. (Original) The stabilized liquid preparation of claim 1, wherein the ionic strength of the liquid preparation is adjusted to greater than 10 mSi by the addition of a salt.

15. (Original) The stabilized liquid preparation of claim 8, wherein the ionic strength of the liquid preparation is adjusted to greater than 10 mSi by the addition of a salt.

16. (Original) The stabilized liquid preparation of claim 1, wherein the protease or its proenzyme is in lyophilized form.

17. (Original) The stabilized liquid preparation of claim 8, wherein the protease or its proenzyme is in lyophilized form.

18. (Original) The stabilized liquid preparation of claim 1, wherein the protease or its proenzyme is present in an amount greater than 0.5 mg/ml.

19. (Original) The stabilized liquid preparation of claim 8, wherein the protease or its proenzyme is present in an amount greater than 0.5 mg/ml.

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20. (Original) A pharmaceutical composition comprising the stabilized liquid preparation of claim 1.

21. (Original) A diagnostic reagent comprising the stabilized liquid preparation of claim 10.

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